

Practitioner's Docket No. MPI98-149P1USRCE2M

09/775,803

IN THE CLAIMS:

This listing of claims will replace all prior versions, and listings, of claims in the application:

1. (Currently amended) A transgenic mouse comprising a modified glycoprotein V (GP V) gene, wherein the mouse has a homozygous modification with at least one allele of said gene has been modified by a construct which removes a sequence of GP V comprising nucleotides encoding Met 1 to Leu 389 of SEQ ID NO:12 and wherein said mouse has platelets with an increased aggregation response to a low concentration of thrombin a decreased bleeding time compared to platelets from a mouse homozygous for the wild type GP V gene.

2. (canceled)

3. (Previously presented) Platelets isolated from blood plasma of the mouse of claim 1.

4. (canceled)

5. (Currently amended) A method of preparing a transgenic mouse comprising a modified glycoprotein V gene, wherein the mouse has a homozygous modification with at least one allele of said gene has been modified by a construct which removes a sequence of GP V comprising nucleotides encoding Met 1 to Leu 389 of SEQ ID NO:12, said method comprising:

a) introducing into embryonic stem cells a nucleic acid molecule ~~encoding a modified GP V gene~~ comprising a construct which removes a sequence of GP V comprising nucleotides encoding Met 1 to Leu 389 of SEQ ID NO:12;

b) generating a transgenic mouse from the cells resulting from step a); and

c) breeding the transgenic mouse to obtain a transgenic mouse homozygous for the modified GP V gene; and

d) determining that the bleeding time of platelets from the homozygous transgenic mouse have an increased aggregation response to a low concentration of thrombin compared to platelets from ~~is less than the bleeding time of~~ a mouse homozygous for the GP V gene.

6. – 9. (canceled)

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10. (Currently amended) A method of preparing a transgenic mouse comprising a nonfunctional glycoprotein V gene, wherein the mouse has a homozygous modification with at least one allele of said gene has been modified by a construct which removes a sequence of GP V comprising nucleotides encoding Met 1 to Leu 389 of SEQ ID NO:12, said method comprising:

- a) introducing into embryonic stem cells a nucleic acid molecule ~~encoding~~ comprising a construct which removes a sequence of GP V comprising nucleotides encoding Met 1 to Leu 389 of SEQ ID NO:12 ~~disrupted or nonfunctional GP V gene~~ and a selectable marker;
- b) identifying and selecting transformed cells;
- c) injecting the transformed cells from step b) into blastocysts; ~~and~~;
- d) generating a transgenic mouse from the blastocysts of step c), wherein the generated transgenic mouse is chimeric for the disrupted or nonfunctional GP V gene and wherein said mouse has platelets with an increased aggregation response to a low concentration of thrombin ~~a decreased bleeding time~~ compared to platelets from a mouse homozygous for the wild type GP V gene;
- e) breeding the chimeric mouse with a wild-type mouse to produce a mouse heterozygotic for the nonfunctional GP V gene;
- f) crossing a heterozygotic mouse produced in step e) with a mouse which is chimeric or heterozygotic for the nonfunctional GP V gene; and
- g) selecting a mouse homozygotic for the nonfunctional GP V gene from the resulting progeny.

11. – 14. (canceled)

15. (Currently amended) A method to identify an agent that modulates a thrombotic response of a transgenic mouse having a modified GP V gene, wherein the mouse has a homozygous modification with at least one allele of said gene has been modified by a construct which removes a sequence of GP V comprising nucleotides encoding Met 1 to Leu 389 of SEQ ID NO:12 and wherein said mouse has platelets with an increased aggregation response to a low concentration of thrombin ~~a decreased bleeding time~~ compared to platelets from a mouse homozygous for the wild type GP V gene,

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comprising the step of exposing the mouse to the agent and determining whether the agent modulates the thrombotic response.

16 - 20 (canceled)

21. (Currently amended) A method of determining the effect of an agent on a characteristic of a mouse that is attributable to the expression of the GP V gene, wherein the mouse has a homozygous modification with at least one allele of said gene has been modified by a construct which removes a sequence of GP V comprising nucleotides encoding Met 1 to Leu 389 of SEQ ID NO:12 and wherein said mouse has platelets with an increased aggregation response to a low concentration of thrombin a decreased bleeding time compared to platelets from a mouse homozygous for the wild type GP V gene, and wherein said characteristic is platelet function, said method comprising;

- a) administering said agent to the mouse of claim 1;
- b) maintaining said mouse for a desired period of time after said administration;
- and,
- c) determining whether the characteristic of said mouse that is attributable to the expression of the modified GP V gene has been affected by the administration of said agent.

22. (canceled)

23. (Currently amended) A cell isolated from a transgenic mouse that comprises a transgene stably integrated into the mouse's genome, said transgene encoding a modified glycoprotein V gene, wherein the mouse has a homozygous modification with at least one allele of said gene has been modified by a construct which removes a sequence of GP V comprising nucleotides encoding Met 1 to Leu 389 of SEQ ID NO:12 and wherein said mouse has platelets with an increased aggregation response to a low concentration of thrombin a decreased bleeding time compared to platelets from a mouse homozygous for the wild type GP V gene.

24. (Currently amended) The cell method of claim 23 5, further comprising the step of introducing the wherein said transgene has been introduced into said mouse or an

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~~ancestor of said mouse~~ via homologous recombination in embryonic stem cells, and
~~further wherein said mouse expresses a modified GP V protein.~~

25. (canceled)

26. (Currently amended) The mouse line of claim 24 1, wherein said mouse is fertile and transmits the modified GP V gene to its offspring.

27. (Currently amended) The mouse line of claim 23 1, wherein the modified GP V protein is nonfunctional.

28. (Currently amended) A method of determining the effect of an agent on a characteristic of a mouse that is attributable to the expression of the GP V gene, wherein the mouse has a homozygous modification with at least one allele of said gene has been modified by a construct which removes a sequence of GP V comprising nucleotides encoding Met 1 to Leu 389 of SEQ ID NO:12 and wherein said mouse has platelets with an increased aggregation response to a low concentration of thrombin a decreased bleeding time compared to platelets from a mouse homozygous for the wild type GP V gene, and wherein said characteristic is hemostasis, said method comprising;

- a) administering said agent to the mouse of claim 1;
- b) maintaining said mouse for a desired period of time after said administration;
- and,
- c) determining whether the characteristic of said mouse that is attributable to the expression of the modified GP V gene has been affected by the administration of said agent.

29. (Currently amended) A method of determining the effect of an agent on a characteristic of a mouse that is attributable to the expression of the GP V gene, wherein the mouse has a homozygous modification with at least one allele of said gene has been modified by a construct which removes a sequence of GP V comprising nucleotides encoding Met 1 to Leu 389 of SEQ ID NO:12 and wherein said mouse has platelets with an increased aggregation response to a low concentration of thrombin a decreased bleeding time compared to platelets from a mouse homozygous for the wild type GP V gene, and wherein said characteristic is coagulation, said method comprising;

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- a) administering said agent to the mouse of claim 1;
- b) maintaining said mouse for a desired period of time after said administration;
and,
- c) determining whether the characteristic of said mouse that is attributable to the expression of the modified GP V gene has been affected by the administration of said agent.

30. (Currently amended) A method of determining the effect of an agent on a characteristic of a mouse that is attributable to the expression of the GP V gene, wherein the mouse has a homozygous modification with at least one allele of said gene has been modified by a construct which removes a sequence of GP V comprising nucleotides encoding Met 1 to Leu 389 of SEQ ID NO:12 and wherein said mouse has platelets with an increased aggregation response to a low concentration of thrombin a decreased bleeding time compared to platelets from a mouse homozygous for the wild type GP V gene, and wherein said characteristic is thrombosis, said method comprising;

- a) administering said agent to the mouse of claim 1;
- b) maintaining said mouse for a desired period of time after said administration;
and,
- c) determining whether the characteristic of said mouse that is attributable to the expression of the modified GP V gene has been affected by the administration of said agent.